UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,484	01/09/2004	Albert M. Van Rhee	018512-009910US	6188

20350 7590 10/18/2006

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
CRAIG, DWIN M	

ART UNIT	PAPER NUMBER
2123	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,484	VAN RHEE, ALBERT M.	
	Examiner	Art Unit	
	Dwin M. Craig	2123	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/9/2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/25/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The information disclosure statement (IDS) submitted on 5/25/2005 fails to comply with the provisions of 37 CFR 1.97, 1.98, CFR 37s1.98 and MPEP § 609, because references A0, lacks a publication date on both the actual copy or on the listing in the submitted PTOS 1449. It has been placed in the application file, but the information referred to therein has not been considered on the merits. Applicant is advised that the date of any of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See CFR 37s1.98 Content of the information disclosure statement, specifically ¶ 5. The other references in the submitted IDS (1449) have been fully considered by the examiner.

Claims herein under examination are 1-16.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-16 are directed towards a method and a computer readable medium comprising a series of mathematical steps for manipulation of datum that is then organized and compared via

a specified criteria equivalent to mental steps. Applicant is reminded that mental processes are not statutory subject matter under 35 USC 101.

The method claims are not statutory as any computer-implemented method must produce a result which is concrete, tangible and useful. As set forth in MPEP 2106(IV)(B):

"In practical terms, claims define nonstatutory processes if they:

-consist solely of mathematical operations without some claimed practical application (i.e., executing a "mathematical algorithm"); or

-simply manipulate abstract ideas, e.g. a bid (Schrader; 22 F.3d at 293-94, 30 USPQ2d at 1458-59) or a bubble hierarchy (Warmerdam, 33 F.3d at 1360, 31 USPQ2d at 1759), without some claimed application."

As the claims in the instant application recite steps to mathematically manipulate data, (claim 1 for example, *using a first recursive partitioning process...determining a consensus compound...*) the claimed method does not produce a tangible, useful result, claims 1-14 do not recite statutory subject matter.

As set forth in MPEP 2106 (IV)(B)(2)(b)(ii):

"A claim is limited to a practical application when a method, as claimed, produces a concrete, tangible and useful result; i.e., the method recites a step of act of producing something that is concrete, tangible and useful result (as in State Street, 149 F.3d at 1373, 47 USPQ2d at 1601) and/or when a specific machine is being claimed (as in Alappat, 33 F.3d at 1544, 31 USPQ2d at 1557 (in banc). For example, a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory.

The MPEP § 2106 (IV)(B)(2)(b)(ii) states the following example:

A computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing the mathematical algorithm is statutory.

Comparing the above discussion to claims 1-14, the claimed method and computer readable medium merely creates a test library, forms models, performs a mathematical algorithm on the models *...recursive partition process...* and then *determines <sic>a consensus compound* using an unspecified criteria, *mental step*. The claimed process falls more into the example of *Warmerdam (bubble hierarchy)*. In this example, the *determination of a consensus compound* fails to provide the required concrete, useful and tangible result. Instead, like the sorting of data using a *bubble hierarchy* merely provides an abstract result with no *concrete tangible and useful* result. Note that there is real question as to the concrete aspect of applicant's claims, because the claim fail to teach the criteria for *determination of the consensus compound* clarity is lacking as to if the claimed algorithm will determine the same compound if the algorithm is repeated.

Claims 1 and 9 are directed towards a computerized method to manipulate libraries of data and models, which is merely manipulating data structures using a computing device, the claims as set forth do not disclose that this process produces a concrete, tangible useful result.

As set forth in MPEP § 2106 (IV)(B)(2)(b)(i)

"Examples of claimed processes that do not achieve a practical application include:

- step of "updating alarm limits" found to constitute changing the number value of a variable to represent the result of the calculation (Parker v. Flook, 437 U.S. 584, 585, 198 USPQ 193, 195 (1978));

- final step of "equating" the process outputs to the values of the last set of process inputs found to constitute storing the result of calculations (In re Gelnovatch, 595 F.2d 32, 41 n.7, 201 USPQ 136, 145 n.7 (CCPA 1979); and

- step of "transmitting electrical signals representing" the result of calculations (In re De Castelet, 562 F.2d 1236, 1244, 195 USPQ 439, 446 (CCPA 1977) ("That the computer is instructed to transmit electrical signals, representing the results of its calculations, does not constitute the type of post solution activity' found in Flook, [437 U.S. 584, 198 USPQ 193 (1978)], and does not transform the claim into one for a process merely using an algorithm. The final transmitting step constitutes nothing more than reading out the result of the calculations.")); and

-step of displaying a calculation as a gray code scale (In re Abele, 684 F.2d 902, 908, 214 USPQ 682, 687 (CCPA 1982))."

Comparing the above examples to claims 1-14, the claimed method merely performs a *determination* and fails even to *update* or *change* the value as a result of a calculation. Further the claimed process does not even disclose the production of a signal or the final step of making equating a result, merely a *determination* is claimed.

Claims 1-16 fail to teach or disclose even the storing in a memory or the display of the *consensus compound*. It is noted that a claim may be statutory when it identifies the physical structure of manufacture in terms of its hardware, or a hardware software combination. Claims 1-14 do not recite any physical or hardware limitations, as set forth above. It is also noted that a claim directed to a product that has a practical application in the arts may be statutory; e.g. a computer comprising a program that produces a concrete, tangible and useful result, as decided

in Alappat (31 USPQ2d 1557) and State Street (47 USPQ2d 1601). As set forth above, the claimed method does not produce a concrete, tangible and useful result, therefore the method comprising a library, a plurality of models, that are recursively partitioned using a computer and the determination of a consensus compound, fail to describe a product and apparatus or form such using a method that would have a practical application in the arts and are thus not statutory.

Therefore, claims 1-16 are considered to be non-statutory subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-16 are rejected under 35 USC 102(b) as being anticipated by, "Retrospective Analysis of an Experimental High-Throughput Screening Data Set by Recursive Partitioning" by A. Michiel van Rhee, Jon Stocker, David Printzenhoff, Chris Creech, P. Kay Wagoner, Kerry L. Spear *hereafter reffered to as van Rhee.*

3.1 As regards independent claims 1 and 9 and using independent claim 1 as an example, *van Rhee* discloses, *a method for screening compounds for biological activity comprising: a) selecting a test library of compounds;*

Page 268 right column under the heading "Methods"...

> A 20 986-member library from our compound inventory was selected and submitted for screening. This chemical library was entirely composed of combinatorial chemistry derived compounds, synthesized either by solid or by liquid phase parallel methods. The biological activity of all library members was determined individually. A set of eight randomly selected plates, accounting for 640 library members, was analyzed by LC/MS. Of the total number of samples analyzed, 81% were found to be better than 80% pure, and 66% were found to be better than 90% pure.

The median, average, and standard deviation values were 94%, 88%, and 15%, respectively. Therefore, the purity of the majority of the library members was deemed to exceed 80%. The combinatorial process was directed by synthetic feasibility without prior knowledge of the biological target. Since the chemical library was set up to take advantage of synthetic feasibility rather than molecular diversity, no diversity analysis prior to compound selection was performed.

The set was mathematically divided into a 5000-member training set based on either diverse selection (DS; D-optimal design strategy) or random selection (RS; iteratively obtained using a random number generator) and into a 15 986-member test set. Biological data were generated in a high-throughput screening (HTS) fashion using a cell based method proprietary to ICAgen, Inc.

b) forming a first analytical model using a first recursive partitioning process using a digital computer, wherein the first recursive partitioning process is performed on at least some of the compounds in the test library of compounds;

c) forming a second analytical model using a second recursive partitioning process using the digital computer, wherein the second recursive partitioning process is performed on at least some of the compounds in the test library of compounds;

Page 268 left column...

Recursive partitioning (RP) is a nonparametric classification technique that has been shown to have applicability in, e.g., a clinical setting.[21-25] In studies designed to identify risk subgroups, RP successfully identified subgroups with distinct risk assessments that had previously not been identified using more traditional logistic regression.[21,26] This finding agrees with our assertion that RP may be able to identify discreet binding modes within an HTS data set. An overview and comparison of various statistical methods, e.g., linear discriminant analysis, logistic regression, nearest neighbor clustering, and recursive partitioning, were presented by Hand several years ago.[23]

With the advent of combinatorial chemistry and HTS, the data structure and organization increasingly seem to more closely resemble a rather disparate patient population than an idealized lead optimization set such as envisioned by Topliss[27,28] and employed by many medicinal chemists. Comparisons of nonparametric recursive partitioning to parametric analyses have been performed[22,25] and generally indicate that RP is significantly better at identifying synergistic and nonlinear relationships, whereas multivariate techniques perform better at late stage analyses...

Page 272 right column...

The cross-validation (XV) experiment led us to investigate how the "information content" of the training set influences the outcome of the analysis. We found that at a low number of XV groups (2 or 3), i.e., high information dilution, the predictivity of the models fell short of the expectations based on a larger number of XV groups (5 or 10). When the XV experiment was run with five XV groups, i.e., 80% of the training set, the model values of the training set and the test set were in good agreement (Table 1). Alternatively, when two XV groups were used, i.e., 50% of the training set, the XV model was less predictive of the full model. A similar effect is seen when the full training set is reduced to 2500 diversely selected compounds from the original 5000-member DS training set. Twoing-7-110 predicted 5.8-fold enrichment, and yielded 4.2-fold enrichment (Table 1), but with rather unstable optimization traces (not shown) and a significant discrepancy between predicted and realized yields.
This less predictive model reflects the loss of information content in the training set selection, and deserves a closer examination.

As regards the different analytical models see Table 1 on page 271 and the descriptive text...

Page 274 Table 2 and the left column...

In an RP model each terminal node represents a different stratification of the data that is not necessarily analogous to, or even consistent with, another node. This opens up the possibility that different nodes may represent differences either in chemical or in biological stratification. We therefore investigated the results for each of the terminal nodes individually. On the basis of a general definition of chemical core structures derived from the combinatorial synthetic process, eight distinct chemotypes could be identified within the training and test sets (CT1 through CT8).

and d) determining a consensus compound set using at least the first analytical model and the second analytical model.

Page 270 right column...

One method, consensus scoring, emphasizes increases in hit rate by eliminating false positives from the prioritization list.[35] The aim of our analysis of HTS data is not simply enhanced hit rates, although it features prominently in the evaluation of the methodology. The aim, as we've chosen to define it, is (1) to increase the efficiency of our primary screens, i.e., increased hit rates; (2) to identify and pursue multiple chemotypes in order to develop compounds along parallel product lines, i.e., to achieve the highest percentage of chemotypes retrieved possible; and (3) the ability to explain nonlinear structure-activity relationships. Other factors such as the cost of a compound collection[36] may also contribute to the overall efficiency of the method, but they are not explicitly considered in this analysis.

Fold enrichment and percent hit recovery are not necessarily independent, rather they are interdependent. As the models become more sophisticated, e.g., increased tree depth, the activity is more narrowly defined, and as a result more false positives (compounds initially incorrectly included as active, but by a more refined model correctly identified as inactive) are eliminated from the model. However, concurrently, the method also eliminates more false negatives (compounds initially correctly identified as active, but subsequently incorrectly classified by the model as inactive), resulting in a better fold enrichment in the remaining models but a lower overall percent hit recovery (Figure 3).

3.2 As regards dependent claims 2 and 10 and using dependent claim 2 as an example, *van Rhee* discloses, *further comprising: forming a third analytical model using a third recursive partitioning process using the digital computer, wherein the third recursive partitioning process is performed on at least some of the compounds in the test library of compounds; and wherein determining the consensus compound set further includes using the third analytical model in addition to the first analytical model and the second analytical model.*

Page 272 right column...

The cross-validation (XV) experiment led us to investigate how the "information content" of the training set influences the outcome of the analysis. We found that at a low number of XV groups (2 or 3), i.e., high information dilution, the predictivity of the models fell short of the expectations based on a larger number of XV groups (5 or 10). When the XV experiment was run with five XV groups, i.e., 80% of the training set, the model values of the training set and the test set were in good agreement (Table 1). Alternatively, when two XV groups were used, i.e., 50% of the training set, the XV model was less predictive of the full model. A similar effect is seen when the full training set is reduced to 2500 diversely selected compounds from the original 5000-member DS training set. Twoing-7-110 predicted 5.8-fold enrichment, and yielded 4.2-fold enrichment (Table 1), but with rather unstable optimization traces (not shown) and a significant discrepancy between predicted and realized yields.
This less predictive model reflects the loss of information content in the training set selection, and deserves a closer examination.

As regards the different analytical models see Table 1 on page 271 and the descriptive text...

Page 274 Table 2 and the left column...

In an RP model each terminal node represents a different stratification of the data that is not necessarily analogous to, or even consistent with, another node. This opens up the possibility that different nodes may represent differences either in chemical or in biological stratification. We therefore investigated the results for each of the terminal nodes individually. On the basis of a general definition of chemical core structures derived from the combinatorial synthetic process, eight distinct chemotypes could be identified within the training and test sets (CT1 through CT8).

3.3 As regards dependent claims 3, 4, 11 and 12 and using dependent claims 3 and 4 as an example, *van Rhee* discloses, *wherein the compounds that are used to form the first and second analytical models are the same, and wherein the compounds that are used to form the first and the second analytical models are different.*

See page 268-269 under the heading "Methods"

3.4 As regards dependent claims 5 and 13 and using dependent claim 5 as an example, *van Rhee* discloses, *wherein the compounds that are used to form the first and the second analytical models are the same and constitute a training set of the library of compounds.*

See pages 267-276 where training sets of data is discussed.

3.5 As regards dependent claims 6 and 14 and using dependent claim 6 as an example, *van Rhee* discloses, *wherein test library of compounds comprise ion channel modulators.*

Page 267 Introduction...

Ion channels are membrane embedded proteins of multimeric composition with intrinsic ion conduction properties. The intended pharmacological endpoint, i.e., activation, prolongation of activation, termination of activation, or block of the target ion channel, is dependent on the site and mode of binding of the ligand to the channel. Consequently, we are forced to reevaluate the leading pharmacological paradigm that we can competitively displace a natural or xenobiotic agent from a binding site. Therefore, to further our understanding of ion channel biology and medicine, we wanted to find an efficient way to identify modulators of multiple ion channel subtypes within ion channel families, so-called gene families, without focusing on a single binding site or mechanism.

3.6 As regards dependent claims 7 and 15 and using dependent claim 7 as an example, *van Rhee* discloses *wherein d) is performed by the digital computer .*

Page 269, *software...*

3.7 As regards dependent claims 8 and 16 and using dependent claim 8 as an example, *van Rhee* discloses, *wherein determining the consensus compound set includes identifying compounds that are predicted to be active by both the first analytical model and the second analytical model.*

Page 273, under the heading "Experimental Results"

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dwin M. Craig whose telephone number is (571) 272-3710. The examiner can normally be reached on 10:00 - 6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paul L. Rodriguez can be reached on (571) 272-3753. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dwin McTaggart Craig

PAUL RODRIGUEZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 2100

10/13/06